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Acknowledgement of receipt

We hereby acknowledge receipt of the following submission by the proprietor:

Submission number	602721
Application number	EP02718994.3
Patent number	EP1392849
Date of receipt	25 June 2009
Your reference	UCH13189OP
Proprietor	University of Chicago
Title	Yeast screens for agents affecting protein folding

Documents submitted

package-data.xml	ep-opposition-data.xml
ep-oppo.pdf (2 p.)	OTHER-1.pdf\Annex A - Consolidated list of documents.pdf (2 p.)
OREX3.pdf\Response to the Communication pursuant to Rule 79(1) EPC.pdf (41 p.)	Published-Evidence-1.pdf\D17 - Temussi et al..pdf (7 p.)
Published-Evidence-2.pdf\D18 - Koo et al.pdf (2 p.)	Published-Evidence-3.pdf\D19 - Outeiro and Lindquist.pdf (9 p.)
Published-Evidence-4.pdf\D20 - Willingham et al..pdf (4 p.)	Published-Evidence-5.pdf\D21 - Cooper et al..pdf (5 p.)
Other-evidence-1.pdf\D15 - EPO form 1205A.pdf (2 p.)	Other-evidence-2.pdf\D16 - EPO Form 1303.pdf (1 p.)

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Submission in opposition proceedings

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Proprietor/representative's reference	UCH13189OP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1392849
Application No.	EP02718994.3
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	02 January 2008
Title of the invention	Yeast screens for agents affecting protein folding
Proprietor of the patent	University of Chicago

Documents attached:

	Description of document	Original file name	Assigned file name
1	Reply to an examination report in opposition proceedings	Response to the Communication pursuant to Rule 79(1) EPC.pdf	OREX3.pdf
2	Any annexes (other than citation) to an opposition letter - Annex A - Consolidated list of documents	Annex A - Consolidated list of documents.pdf	OTHER-1.pdf

Evidence filed subsequently:

D15	Other evidence	EPO form 1205A (01.02) pertaining to EP 00 977 270 (i.e., D7) original file name: D15 - EPO form 1205A.pdf attached as: Other-evidence-1.pdf
D16	Other evidence	EPO Form 1303 (11.97) pertaining to EP 00 977 270 (i.e., D7) original file name: D16 - EPO Form 1303.pdf attached as: Other-evidence-2.pdf

D17	Non-patent literature - article	Temussi, Piero Andrea et al., "From Alzheimer to Huntington: why is a structural understanding so difficult?" EMBO Journal, 2003 particular relevance: 355-361 original file name: D17 - Temussi et al..pdf attached as: Published-Evidence-1.pdf
D18	Non-patent literature - article	Koo, Edward H. et al., "Amyloid diseases: Abnormal protein aggregation in neurodegeneration" Proc. Natl. Acad. Sci. USA, 1999 particular relevance: 9989-9990 original file name: D18 - Koo et al.pdf attached as: Published-Evidence-2.pdf
D19	Non-patent literature - article	Outeiro, Tiago et al., "Yeast Cells Provide Insight into Alpha-Synuclein Biology and Pathobiology" Science, 2003 particular relevance: 1772-1775 original file name: D19 - Outeiro and Lindquist.pdf attached as: Published-Evidence-3.pdf
D20	Non-patent literature - article	Willingham, Stephen et al., "Yeast Genes That Enhance the Toxicity of a Mutant Huntingin Fragment or alpha-Synuclein" Science, 2003 particular relevance: 1769-1772 original file name: D20 - Willingham et al..pdf attached as: Published-Evidence-4.pdf
D21	Non-patent literature - article	Cooper, Antony A. et al., "alpha-Synuclein Blocks ER-Golgi Traffic and Rab1 Rescues Neuron Loss in Parkinson's Models" Science, 2006 particular relevance: 324-328 original file name: D21 - Cooper et al..pdf attached as: Published-Evidence-5.pdf

Signatures

Place:	Munich, Germany
Date:	25 June 2009
Signed by:	DE, df-mp, S. Pohlman 13690
Capacity:	(Representative)

European Patent Office
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June 25, 2009

Opposition against European patent EP 1 392 849 (Application No. 02 718 994.3)
Title: Yeast screens for agents affecting protein folding
Proprietor: University of Chicago
Opponent: reMynd N. V.
Our Ref.: UCH13189OP

In response to the Communication pursuant to Rule 79(1) EPC dated December 19, 2008, we herewith provide our observations on the opposition filed by

reMynd N.V. ("Opponent" or "O").

For the further proceedings, we suggest using the enclosed consolidated list of documents (**Annex A**), which we believe to contain all documents filed by the Opponent.

Each of the documents is given a consecutive number to aid reference to the documents filed by the Opponent and by us.

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A. REQUESTS

1. We request that the patent be maintained as granted (*i.e.*, our Main Request)

2. We request that the opposition be rejected.

3. We request to be allowed to file Auxiliary Requests during the opposition proceedings, if deemed necessary.

4. In case the Opposition Division ("OD") cannot decide the matter in favour of the Proprietor on the basis of the written submissions, we request oral proceedings pursuant to Article 116 EPC.

5. In case oral proceedings take place, we kindly request that the Opposition Division provides beforehand a preliminary opinion on the issues to be discussed during the oral proceedings.

B. THE GRANTED CLAIMS DO NOT CONTAIN ADDED MATTER (ARTICLE 123(2) EPC)

1. In items 3.7.1 and 3.7.2 of its brief, O alleges that claims 1 and 9 would breach Article 123(2) EPC, since the application as filed would not provide support for these claims.

   Specifically, O seems to contend that method claims 1 and 9 contain new matter because of (i) reciting in the preamble of the claimed methods the phrase "compound that decreases alpha synuclein-associated toxicity", while the original application disclosed "methods for identifying therapeutic agents" and (ii) omitting in claim 9 method steps that are disclosed in the original application, thereby inadmissibly broadening the claim.

2. The Proprietor disagrees, since the application as filed fully supports claims 1 and 9.

   In setting forth his allegations, O seems to forward a "selected reading approach" , which neglects the commonly applied *whole contents approach* for assessing compliance with the requirements of Article 123(2) EPC.

   In particular, we emphasize that the application as filed must be read as a whole *with a mind willing to understand* and to make technical sense out of it. In fact, it is established in the case law pertaining to Article 123(2) EPC that the relevant question in assessing whether an amendment adds subject-matter extending beyond the content of the application is whether or not the amended subject matter would be directly and unambiguously derived by the skilled person from the application. This determination takes account of the whole content of the document as understood by the skilled person when reading the document with common general knowledge.

   For example, an Appeal Board in T 1269/06 held that, for the assessment of whether, contrary to Article 100(c) EPC, the subject matter of the patent extends beyond the content of the application as filed, the key question is whether the amendments made in the description, or – as in the case at issue – the claims, indeed provided the skilled person with additional, technically relevant information which was not contained in the original application documents. There is no inference of added matter that results from the fact that terms not present in the claims at the filing date were subsequently introduced from the description. Also, the added matter inquiry does not involve a purely semantic analysis of the contested passages. Instead, the party raising the objection must be able to identify clearly the technical teaching that allegedly extends beyond the content of the original disclosure.

   However, O completely fails to identify any new technical teaching that was added in claims 1 and 9 over the original application as will be demonstrated in the following.

2.1 Claim 1 reads

> A method of screening for a compound that decreases alpha synuclein-associated toxicity, the method comprising the following steps:
>
> a) contacting a yeast cell with a candidate compound, wherein the yeast cell expresses a polypeptide comprising alpha synuclein;
> b) contacting the yeast cell with a toxicity-inducing agent; and
> c) evaluating the yeast cell for viability,
>
> wherein viability indicates that the candidate compound decreases alpha synuclein-associated toxicity.

Claim 1 takes its basis from original claims 30, 54 and 55 in conjunction with page 3, lines 19-22; the paragraph bridging pages 7 and 8; page 8, lines 9-12; as well as from page 52, lines 24-25; page 7, lines 14-15; and page 6, lines 14-21 of the application as filed.

> 30. A method of screening for a therapeutic agent for Parkinson's disease comprising:
>
> a) contacting a yeast cell expressing a polypeptide comprising an alpha synuclein polypeptide with a composition comprising a toxicity inducing agent;
> b) contacting the yeast cell with a candidate compound; and
> c) evaluating the yeast cell for viability, wherein viability indicates the candidate compound is a candidate therapeutic agent.
>
> 54. A method of screening for a therapeutic agent for a protein misfolding disease comprising:
>
> a) contacting a yeast cell with a candidate compound, wherein the yeast cell expresses a polypeptide comprising a misfolded disease protein;
> b) contacting the yeast cell with a toxicity inducing agent;
> c) evaluating the yeast cell for viability, wherein viability indicates the candidate compound is a candidate therapeutic agent.
>
> 55. The method of claim 54, wherein the protein misfolding disease is Alzheimer's disease, Parkinson's disease, a Prion disease, Familial Amyloid Polyneuropathy, a Tauopathy, or a Trinucleotide disease.

Page 3, lines 19-22 of the application as filed discloses "misfolded disease proteins" which are expressed by a yeast cell:

Conditions and/or agents have been identified that induce toxicity ("toxicity inducing agent") in a yeast cell expressing a misfolded disease protein, such as huntingtin or alpha synuclein, which are associated with Huntington's disease and Parkinson's disease, respectively.

Pages 7 and 8, bridging paragraph of the application as filed reflect the embodiments covered by original claims 30, 54 and 55:

> The present invention further encompasses methods of screening for a therapeutic agent for a protein misfolding disease comprising: a) contacting a yeast cell with a candidate compound, wherein the yeast cell expresses a polypeptide comprising a misfolded disease protein; b) contacting the yeast cell with a toxicity inducing agent; c) evaluating the yeast cell for viability, indicating the candidate compound is a candidate therapeutic agent. In some embodiments, the protein misfolding disease is Alzheimer's disease, Parkinson's disease, a Prion disease, Familial Amyloid Polyneuropathy, a Tauopathy, or a Trinucleotide disease. It is specifically contemplated that the protein misfolding disease may a Trinucleotide disease, such as Huntington's disease. In other embodiments the misfolded disease protein is huntingtin, β-amyloid, PrP, alpha synuclein, synphilin, transthyretin, Tau, ataxin 1, ataxin 3, atrophin, or androgen receptor.

Page 8, lines 9-12 of the application as filed discloses further toxicity-inducing agents:

> It is also contemplated that the toxicity inducing agent may a carbon source, nitrogen source, salt, metal, chemotherapeutic agent, alcohol, translation inhibitor, NSAID, DNA intercalator, chelator, liposome, antibiotic, vitamin, proteasome inhibitor, anti-oxidant, or reducing agent.

As regards the feature that the screening method is for a compound "that decreases alpha synuclein-associated toxicity" reference is made to page 52, lines 24-25

> The yeast-based screening system developed herein is amenable to such screens, and one may directly identify compounds that decrease the toxicity of misfolded disease proteins.

A "misfolded disease protein" is, for example, alpha synuclein; see page 3, lines 19-22 of the application as filed; see also the above quotation.

Page 7, lines 14-15 of the application as filed provides, with respect to determining viability:

> Generally speaking, all of the methods of the present invention may include controls that involve comparing yeast cells in the present and absence of candidate compounds, as well

And page 6, lines 20-21 states:

inducing agent. Absolute or relative viability in the presence of the candidate compound indicates the candidate compound is a candidate therapeutic compound.

In sum, claim 1 is fully supported by the application as filed and, thus, meets the requirements of Article 123(2) EPC.

2.2 Claim 9 reads:

> A method of screening for a compound that decreases alpha synuclein-associated toxicity, the method comprising the following steps:
>
> a) providing a yeast cell engineered to express a polypeptide comprising alpha synuclein;
> b) contacting the yeast cell with a candidate compound; and
> c) evaluating the yeast cell for viability,
>
> wherein an increase in viability of the yeast cell as compared to viability of the yeast cell in the absence of the candidate compound indicates that the candidate compound decreases alpha synuclein-associated toxicity.

Claim 9 takes its basis from page 11, lines 15-22 and lines 30-33; page 12, Table 1; page 52, lines 24-25; page 3, lines 19-22 and lines 27-32; as well as from page 10, lines 30-33; page 67, lines 6-12; and page 7, lines 14-15 of the application as filed.

Generally, on page 10, lines 30-33 it is disclosed that

> FIG. 3. Expression of alpha-synuclein fused to GFP under the control of the GAL1-10 promoter. Expression of WT and A53T is toxic to the cells. Similar phenotypes were observed with alpha-synuclein alone. These assays have been used in the screening methods to identify agents that can alleviate the observed toxicity.

Thus, this passage reflects the gist of the invention claimed in claim 9, which is that expression of alpha-synuclein in yeast can lead to cell death of yeast ("similar phenotypes were observed with alpha-synuclein alone") and that this phenotype can be used to screen for candidate compounds for decreasing alpha-synuclein associated toxicity, if a candidate compound can, e.g., revert or inhibit the toxic phenotype ("these assays have been used in the screening methods to identify agents that can alleviate the observed toxicity").

Page 11, lines 15-22 of the application as filed provides support for "providing a yeast cell engineered to express a polypeptide comprising alpha synuclein" in a method for screening candidate therapeutic agents that prevent and/or inhibit the process of protein aggregation leading to fibrillogenesis and protein deposition:

> The present inventors have developed a system which allows the rapid identification of candidate therapeutic agents that prevent and/or inhibit the process of protein aggregation leading to fibrillogenesis and protein deposition. The system is a yeast-based system, wherein a yeast cell is engineered to expresses a protein or polypeptide that is involved in fibril formation, for example, the yeast cell can express a huntingtin polypeptide in the case of Huntington's disorder, or expresses an alpha synuclein polypeptide in the case of Parkinson's disease, or express an amyloid protein in the case of a disease involving amyloidoses (also see Table 1 for a list of proteins that are associated with fibril formation).

Page 11, lines 30-33 of the application as filed provides support for "contacting a yeast cell with a candidate compound":

> Thus, if such a yeast cell is exposed to a candidate substance, one can screen for the potential of the agent to reverse cytotoxicity, which correlates to the ability of the agent to prevent cytotoxic and/or neurotoxic protein aggregation and fibril formation.

Page 52, lines 24-25 and page 3, lines 19-22 of the application as filed provides support for "a method of screening for a compound that decreases alpha synuclein-associated toxicity":

> The yeast-based screening system developed herein is amenable to such screens, and one may directly identify compounds that decrease the toxicity of misfolded disease proteins.

At page 8, lines 7-9, it is explained that a "misfolded disease protein" is, for example, alpha synuclein:

> In other embodiments the misfolded disease protein is huntingtin, β-amyloid, PrP, alpha synuclein, synphilin, transthyretin, Tau, ataxin 1, ataxin 3, atrophin, or androgen receptor.

Page 7, lines 14-15 of the application as filed provides support for a "negative control" as referred to in the "wherein clause" of claim 9:

> Generally speaking, all of the methods of the present invention may include controls that involve comparing yeast cells in the present and absence of candidate compounds, as well

Moreover, page 6, lines 20-21 refer to the indication of viability as one that is absolute or "relative", the latter term indicating to the skilled person that a comparison is to be made, i.e., in the sense of a comparison with a control.

Page 3, lines 27-32 of the application as filed provides further support for the "read-out" feature of claim 9 given in the "wherein clause":

> The screen uses viability of the yeast, which express a misfolded disease protein and in which toxicity is induced, to identify compounds that have therapeutic potential in the treatment of the disease associated with the misfolded disease protein. An advantage of the screening methods is that an understanding of the physiology and/or cell biology of the misfolded disease protein or of the etiology of a misfolded protein disease is not necessary to identify candidate therapeutic compounds.

In fact, in one embodiment, "toxicity is induced" in a yeast by expressing alpha synuclein; see page 10, lines 31-33 of the application as filed:

> GAL1-10 promoter. Expression of WT and A53T is toxic to the cells. Similar phenotypes were observed with alpha-synuclein alone. These assays have been used in the screening methods to identify agents that can alleviate the observed toxicity.

Furthermore, it is noted that Example 11, page 67, lines 6-7 of the application as filed refers to compounds that "exhibited an ability to alleviate toxicity caused by alpha-synuclein overexpression".

Additional support for the "read-out" feature can be found on page 6, lines 8-12 and page 7, lines 14-18 and 18-20 of the application as filed:

> Increased viability by the yeast cell contacted with the candidate compound compared the yeast cell not contacted with the candidate compound indicates that the candidate compound is a candidate therapeutic agent. In other words, as with other embodiments of the invention, absolute or relative viability (increased) in the presence of the candidate compound indicates the candidate compound is a candidate therapeutic compound.
>
> Generally speaking, all of the methods of the present invention may include controls that involve comparing yeast cells in the present and absence of candidate compounds, as well as yeast cells in the presence and absence of toxicity inducing agents or toxicity inducing conditions. It is contemplated that any compositions or methods discussed with respect to one embodiment may be employed in the context of other embodiments.

The passages above show that the subject matter of granted claim 9 (as well as granted claim 1) may be directly derived from the original application. The skilled person would appreciate that though there may be a slight change in wording, there has been no change in substance with respect to the original application.

Finally, we would like to address the allegations made on pages 18-19 by O that the claims are not supported due to certain embodiments disclosed on page 11 and pages 48-49 of the description. However, these cited passages are taken out of context and when read in context, it is clear that they describe specific alternative embodiments of the invention, without limiting the invention as disclosed. Clearly, one embodiment of the invention is a yeast cell expressing alpha-synuclein, as may be taken from the original claims and passages cited above.

In sum, claim 9 is fully supported by the application as filed and, thus, meets the requirements of Article 123(2) EPC.

C. THE GRANTED CLAIMS ARE ENTITLED TO THE PRIORITY DATE (ARTICLE 89 EPC)

1. In item 3.2 of its brief, O refrains from contesting the priority claim "at this time" and reserves "the right to contest the priority claim at a later stage".

2. However, in order to forestall the O in contesting the priority claim, we provide the following Table detailing where examples of support for all granted claims can be identified in the priority document (i.e., US 60/269,157).

Claim Number	Examples of support in the priority document
1	Claims 30, 54, 55 and 58; p. 3, ll. 21.24; p. 7, ll. 20-26; p. 9, ll. 9-16; p. 57, ll. 12-14; p. 8, ll. 22-25
2	p. 9, ll. 20-23
3	p. 9, ll. 20-23
4	p. 20, ll. 20-22
5	p. 23, 10th row from the bottom
6	p. 7, ll. 28-29
7	p. 7, ll. 30-31
8	p. 8, ll. 1-2
9	p. 4, ll. 21-24: p. 4, l. 28-p. 5, l.3; p.12, ll. 1-10 and 18-21; p.12, Table 1, 3rd row; p. 57, ll. 12-14; p.11, ll.16-18
10	p. 12, ll. 10-13
11	p. 7, ll. 28-29
12	p. 7, ll. 30-31
13	p. 8, ll. 1-2

From the above it is immediately apparent that the granted claims are entitled to the priority date and, thus, the priority date of February 15, 2001 is the filing date of the granted patent (Article 89 EPC).

Consequently, only documents cited by O that are published prior to the priority date of the patent are full prior art pursuant to Article 54(2) EPC.

D. THE GRANTED CLAIMS ARE NOVEL (ARTICLE 54 EPC)

1. Novelty of claim 9 vis-à-vis WO 01/23412 (D7)

Clearly, O's novelty attack of claim 9 (see item 3.3.1 of O's brief) in view of **D7** has no legal basis.

Indeed, **D7** is not, contrary to the incorrect assertion by O, a document pursuant to Article 54(3) EPC.

At the time when **D7** would have been due for entering the regional phase before the EPO, the requirements of Article 158(2) EPC 1973[1] were not fulfilled (see **D15**, *i.e.*, EPO Form 1205A "Noting of Loss of Rights").

Moreover, as evidenced by **D16**, *i.e.*, EPO Form 1303 (11.97) the applicants of **D7** did not make use of any of the legal remedies available and, thus, the application is (finally) deemed to be withdrawn.

Therefore, in accordance with Article 158(1) EPC 1973, **D7** is not prior art pursuant to Article 54(3) EPC.

In detail, Article 158(1) EPC required that

> "Publication under Article 21 of the Cooperation Treaty of an international application for which the European Patent Office is a designated Office shall, subject to paragraph 3, take the place of the publication of a European patent application and shall be mentioned in the European Patent Bulletin. **Such an application shall not however be considered as comprised in the state of the art in accordance with Article 54, paragraph 3, if the conditions laid down in paragraph 2 are not fulfilled.**" [Emphasis added]

However, as evidenced by **D15** the conditions laid down in paragraph 2 (*i.e.*, Article 158(2) EPC 1973) as referred to in Article 158(1) EPC1973[1] are not fulfilled by **D7**.

Hence, **D7** is not a prior art pursuant to Article 54(3) EPC for the patent.

Consequently, it is evident that claim 9 is novel vis-à-vis **D7**.

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[1] Article 158(2) EPC1973 required that the international application shall be supplied to the European Patent Office in one of its official languages and that the applicant shall pay to the European Patent Office the national fee provided for in Article 22, paragraph 1, or Article 39, paragraph 1, of the Patent Cooperation Treaty.

2. Novelty of claim 9 vis-à-vis WO 01/06989 (D8)

2.1 In item 3.3.1 of its brief, O asserts that **D8,** which is said to be prior art under Article 54(2) EPC for the opposed patent, would disclose "a method of screening for a compound comprising the steps of:

- providing a yeast cell engineered to express a polypeptide comprising alpha synuclein;
- contacting the yeast cell with a candidate compound; and
- evaluating the yeast cell for viability

which corresponds to characterizing steps (a) to (c) of the screening method of claim 9".

O makes reference to page 25, line 30 to page 31, line 4; partially to page 25, lines 31-32; page 25, lines 37-38; page 26, line 2; page 26, lines 12-15; and page 28, lines 21-22 and 24-25 of **D8**.

2.2 We disagree and submit that O misconstrues the disclosure of **D8**.

Article 54(2) EPC defines the state of the art as comprising "everything made available to the public by means of a written or oral description, by use or in any other way". In this regard, the term "available" has to be interpreted such that, for lack of novelty to be found, all the technical features of a claim in combination must have been communicated to the public.

It is a fundamental principle that a conclusion of lack of novelty must not be reached unless the prior document contains a clear and unambiguous disclosure for the skilled person of the subject matter of the later invention.

Taking these principles into account, an accurate review of D8's disclosure should lead to the conclusion that this document completely fails to disclose the method of claim 9.

The technical disclosure in a prior art document has to be considered in its entirety as it would be done by the person skilled in the art. It is *not* justified to arbitrarily shed light only on isolated parts of such prior art documents, which are distinct from the integral teaching of the respective document and solely serve the Opponent's purpose (see, for example, T 56/87). Moreover, explicit features recited in the claims are not to be ignored.

Specifically, claim 9 reads:

> A method of screening **for a compound that decreases alpha synuclein-associated toxicity**, the method comprising the following steps:

a) providing a yeast cell engineered to express a polypeptide comprising alpha synuclein;
b) contacting the yeast cell with a candidate compound; and
c) evaluating the yeast cell for viability,

wherein an increase in viability of the yeast cell as compared to viability of the yeast cell in the absence of the candidate compound indicates that the candidate compound decreases alpha synuclein-associated toxicity.

[Emphases added]

However, **D8** fails to disclose that a screening method disclosed therein is "*for a compound that decreases alpha synuclein-associated toxicity*".

This is, for example, apparent from page 4, lines 16-27, quoted below:

> In a fifth aspect, the invention provides a method for identifying a compound which specifically recognizes a polypeptide capable of forming undesired intracellular polypeptide aggregates or complexes including, providing a polypeptide capable of forming intracellular polypeptide aggregates; providing a test polypeptide binding molecule, *e.g.*, an intrabody or functional fragment thereof, that binds the polypeptide; incubating the polypeptide and intrabody fragment or fragment thereof with a binding molecule; and determining the ability of the test compound to alter the binding of the polypeptide binding molecule, *e.g.*, an intrabody or functional fragment thereof, wherein those binding molecules that bind the intrabody are eliminated, thereby identifying the test compound as capable of interacting with a polypeptide capable of forming intracellular polypeptide aggregates. In a preferred embodiment, the method is applied, and can be reapplied, to a variegated library of at least 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, and, preferably, 10^9 or more different binding molecules.

and page 25, lines 30-35 to which O makes reference.

> The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate binding molecules (*e.g.*, peptides, peptidomimetics, small molecules, or other drugs) which bind to the target polypeptide, *e.g.*, a huntingtin polypeptide. The method is conducted *in situ*, within cells that exhibit abnormalities that present a model of the given disease. Thus the ability to counteract pathological aggregation of the target polypeptide *in situ*, provides a prerequisite for further therapeutic development.

Thus, **D8** discloses screening assays for identifying modulators which bind to a target protein being capable of aggregation, such as alpha synuclein (page 26, line 2) and alter the ability of the target protein to interact with an intrabody that binds the target protein.

However, this purpose is completely different from that referred to in claim 9.

It is an established principle in the EPO's jurisprudence that the purpose of a claimed method is a functional feature meaning that the method is suited for *that* very purpose which thus defines one of the method steps.

This is illustrated in T 848/93. The application claimed a process which differed from the prior art only in its use (remelting instead of vapour phase soldering). The Examining Division had understood the claim to mean that the process claimed was suitable for the use described, and had considered that it lacked novelty because the process known in the prior art was also suitable for that use, *even if this was not expressly stated.*

However, the Board did not agree. According to the Board in that case, if a claim concerned, for example, an apparatus which differed from a known apparatus only with regard to the use indicated, then the use was not limiting for an apparatus feature. Thus, in such a case, both apparatuses were considered identical in terms of structure. If the known apparatus was suitable for the claimed use, the application lacked novelty. If the claim was directed to an object, a substance or a composition, the same applied. If, however, the claim was for a process, the situation was not comparable. In such a case, the use feature was a functional process feature comparable in category with the other features (steps) of the process. This principle is fully applicable in the present situation.

We note that the principle for assessing novelty of method claims by taking into account the purpose of the method was confirmed in a number of subsequent decisions, e.g., T, 827/04 (item 9 of the Reasons), as well as T 1424/04, T 62/02 or T 1104/99.

Furthermore, in decisions G 2/88 and G 6/88 the Enlarged Board held that a functional feature in a use claim should be construed as a functional technical feature (G 6/88, Reasons 7.1). Although the above decisions of the Enlarged Board discuss "use" claims, it is also pointed out that use claims and method claims are in essence both directed to a process, and thus, the reasoning given in the above decisions of the Enlarged Board is also applicable for other method claims (cf. G 6/88, Reasons 2.2 to 2.5; T 848/93, Reasons 3.3; as well as Guidelines C-III, 4.9).

In the present case, it follows that the method for screening for a compound that decreases alpha synuclein-associated toxicity, in particular the "read-out" of an increase in viability of a yeast cell is thus a technical feature defining the scope of the claim. Moreover, in claim 9, aside from the purpose feature of the method claim, a step of the method is recited as "wherein an increase in viability of the yeast cell as compared to viability of the yeast cell in the absence of the candidate compound indicates that the candidate compound decreases alpha synuclein-associated toxicity", which step further distinguishes over D8.

It follows that the method disclosed in D8 is not novelty-destroying. O's reference to page 25, lines 36-38 is misplaced, since this disclosure concerns a method for screening of compounds that *alter* the undesired accumulation, complexing, or aggregation of a selected polypeptide such as alpha synuclein by applying an intrabody.

> In particular, one method of the invention involves the use of an intrabody in a cell of a non-human subject for the screening of compounds that alter the undesired accumulation, complexing, or aggregation of a selected polypeptide.

Likewise, O's reference to page 26, lines 11-15 is not helpful, since "a change in levels of cell death" as a read-out for an alteration in the "intrabody/polypeptide" interaction does not equate to "evaluating the yeast cell for viability, wherein an increase in viability of the yeast cell as compared to viability of the yeast cell in the absence of the candidate compound indicates that the candidate compound decreases alpha synuclein associated toxicity."

Contrary to O's assertion that it is "redundant as it is clear to the skilled person that a compound which reduces cytotoxicity will increase viability compared to cells without the compound" , this process step is a true technical feature and contribution. Indeed, the present inventors found that an understanding of the physiology and/or cell biology of the misfolded alpha synuclein protein or of the etiology of a protein misfolding disease is not necessary to identify candidate therapeutic compounds.

Accordingly, the viability of a yeast cell can be used to screen for a compound that decreases alpha synuclein-associated toxicity and is thus a technical feature which is not disclosed in the prior art.

Furthermore, O's reference to page 28, lines 21-23 is misplaced:

> In one embodiment, an assay is a cell-based assay in which a cell which expresses a target polypeptide, *e.g.*, huntingtin and an intrabody is contacted with a test compound and the ability of the test compound to alter the polypeptide/intrabody interaction is determined. Tl

Namely, this disclosure envisages a cell-based assay with a cell expressing a target polypeptide and an intrabody, whereby a test compound alters interaction between the target polypeptide and the intrabody. Indeed, the hallmark of the methods disclosed in **D8** is the use of an intrabody. The application states, in relevant part:

> The present invention is based on the discovery that contacting intracellular, pathological huntingtin polypeptide with an intrabody can prevent a hallmark of its abnormal pathology, the formation of polypeptide aggregates. Moreover, such intrabodies can both

(see e.g. page 3, lines 11-13 of **D8**).

As the intrabody is presented as an essential feature of **D8**'s method, it may not be simply ignored when assessing novelty.

However, claim 9 does not refer to a yeast cell that expresses an intrabody. Indeed, the invention of claim 9 does away with the need to asses the intrabody/protein interaction and instead simply looks for increased viability as compared to the control. The considerations in the Board of Appeal decision T 841/04 (see item 6.2 of the reasons, where the Board read in the whole context and purpose of the prior art document a requirement of a different structure for the prior art "tissue equivalent" as compared to the claimed tissue treatment composition; see also novelty considerations in decision T 500/89).

Moreover, the cited disclosure on page 28 purports to employ a yeast cell in a cell-based assay, aimed at identifying a compound which alters the polypeptide/intrabody interaction. Yet, the method of claim 9 concerns a screening method with a different purpose; see above. The passage cited on page 28 is the only instance where **D8** mentions a "yeast cell." Nothing in this passage or anything else in **D8** would have conveyed to the skilled person that expression of alpha synuclein in yeast would be toxic or that a yeast cell expressing alpha synuclein should be used in a viability assay. Also, with respect to this disclosure, it is established case law of the EPO Boards of Appeal that what constitutes the disclosure of a document is governed not merely by the words actually used in its disclosure, but also what the publication reveals to the skilled person as a matter of technical reality (see, e.g., T 412/91). It is also established case law of the EPO that each part of a document needs to be construed in the context of the document as a whole (see, e.g., T 312/94). We note that looking at D8 as a whole, the skilled person would consider the single fleeting suggestion of using yeast cells as having no basis in technical reality (at least insofar as it relates to the O's allegation that D8 conveys the notion of performing a viability assay in yeast expressing alpha synuclein). In contrast to the single reference to yeast cells in **D8**, the rest of the document teaches and exemplifies the use of several animal cells and models (see, e.g., page 26, line 30 to page 27, line 7; and Examples 1, 3-5, and 7). However, nowhere in **D8** is there any experiment showing the use of a yeast cell in any assay. The Background section of **D8** teaches that polypeptides harbouring polygutamine repeats are ubiquitously expressed in human cells and at its highest concentrations in neuronal cells of the cortex and striatum (see, page 2, lines 1-5, 11-17 and 31-38). Given the fact that these proteins are primarily expressed in neuronal cells of a human, the skilled person would have had no reason to consider the single suggestion in **D8** of using yeast cells as somehow being related to the performance of a viability assay in yeast expressing alpha synuclein.

In sum, **D8** plainly fails to disclose each and every feature of claim 9. In particular, it fails to anticipate the purpose of the claimed method and the essential read-out step in the "wherein clause" of claim 9.

For the sake of completeness and to pre-empt further assertions from O that **D8**, although not explicitly disclosing the purpose of the claimed method and the "wherein clause", would inherently disclose these features, we note that a line must be drawn between what has in fact been made available and what remains hidden.

It is thus of no relevance what may have been inherent in what is made available by the prior art as the question of inherency does not arise as such under Article 54 EPC (see also G 2/88, point 10.1 of the reasons for the decision). It is further of **no** relevance what might be inferred from what has been made available. Even "high probability" for an alleged disclosure is not accepted by the Technical Boards of Appeal (see, e.g., T 464/94, repeatedly confirmed by later decisions).

Clearly, for a document to be novelty destroying, it must disclose all features of the claimed method. This is not the case for **D8**. Namely, in deciding what is or is not the inevitable outcome of an express literal disclosure in a particular prior art document, the standard of proof is much stricter than the balance of probability: the "beyond all reasonable doubt" standard needs to be applied.

It follows that if any reasonable doubt exists as to what might or might not be the result of carrying out the literal disclosure and instructions of a prior art document, in other words if there remains a "grey area", then the argument on anticipation based on such a document must fail[2].

Thus, claim 9 is novel over **D8**.

[2] The above arguments that **D8** fails to disclose each and every element of claim 9 and that the principle of inherent disclosure is not available are equally applicable to **D7**, *mutatis mutandis*, just in case O wishes to refer to **D7** in an attempt to attack novelty of claim 9 under Article 54(2) EPC by neglecting the valid priority entitlement of this claim.

E. THE GRANTED CLAIMS ARE INVENTIVE (ARTICLE 56 EPC)

1. In item 3.4 of its brief, O alleges that

   (i) claim 1 lacks inventive step in view of the disclosure of WO 01/06989 (**D8**), optionally combined with Ostrerova-Golts (**D9**) (item 3.4.1);

   (ii) claim 9 lacks inventive step over WO 99/29891 (**D1**) combined with Engelender (**D10**) (item 3.4.2a);

   (iii) claims 9-11 lack inventive step over WO 99/29891 (**D1**) combined with Ostrerova (**D11**) (item 3.4.2b);

   (iv) claim 9 lacks inventive step over WO 99/06545 (**D12**) combined with WO 01/06989 (**D8**) (item 3.4.2c);

   (v) all claims lack inventive step over WO 99/29891 (**D1**), WO 01/06989 (**D8**), WO 99/06545 (**D12**), Krobitsch (**D13**) or Liu (**D14**) or combinations thereof (item 3.4.3); and

   (vi) claim 9 would not solve the problem (item 3.4.2d).

2. We disagree with each of O's allegations and will demonstrate in the following that none of O's attempts to challenge inventive step has any merit.

2.1 THE CONTRIBUTION OF THE PRESENT INVENTION TO THE ART

Before the priority date of the patent, it was the prevailing opinion in the art that knowledge of at least the three dimensional structure of proteins deemed to be involved in a protein misfolding disease such as Huntington, Alzheimer's disease or Parkinson's disease in their healthy and misfolded forms was necessary to understand the pathologies of the disease. Hence, scientists believed that such research was required in the field of protein misfolding diseases to first identify the mechanism of these diseases before any suitable compounds for treatment or prevention could be found; see, for example, Temussi (**D17**).

Moreover, it was believed that for studying these diseases an understanding of the physiology and/or cell biology of the misfolded disease protein was necessary; see, for example, Koo (**D18**) and **D8**.

It was also believed that either animal models or neuronal cells are the method of choice in order to understand the etiology of the misfolded protein disease. (see, e.g., **D2** and **D8**, in particular examples discussed below). Putting it differently, it was believed that in order to understand the protein misfolding disease with the aim of identifying potential therapeutics, a model system as close as possible to the diseases would have to be applied.

However, contrary to what was believed in the art and could have been expected, the invention described in the patent is based, at least in part, on the inventors' discovery that yeast cells expressing alpha synuclein (a protein associated with alpha synucleinopathies such as Parkinson's disease) can exhibit reduced viability. This reduction in viability can be exploited to screen for compounds that alleviate toxicity resulting from alpha synuclein expression in yeast cells (see patent at page 3, lines 5-15).

Hence, an understanding of the mechanism by which alpha synuclein contributes to a disease such as Parkinson's disease is neither critical nor required to put the claimed screening methods into practice. Rather, it is a distinct advantage of the claimed screening methods that a complete understanding of the mechanism of action of alpha synuclein is not required to identify useful compounds (see patent at page 3, lines 15-17).

For the simple reason that yeast cells do not have a nervous system and thus neuronal cells, a skilled artisan would not have considered yeast cells to be the cells of choice to study the effect of alpha synuclein on cell viability.

Thus, it is surprising that the present inventors have chosen yeast cells and used them as "living test tubes" by supplementing them with the gene encoding the human alpha synuclein protein.

They observed that yeast cells lose viability and may die from the same protein that harms dopamine-producing neurons in Parkinson's disease. Thus, the findings of the present inventors speed up the search for new therapeutics for complex brain diseases, such as Parkinson's disease, which are difficult to study in animal models or in neuronal cell cultures. Indeed, the screening methods developed by the present inventors allow a cost efficient, high-throughput screening within a short period of time for potential candidates useful for treating or preventing protein misfolding diseases, such as Parkinson's disease.

The present inventors could in view of their observations provide a system that may be readily manipulated and thus provides the opportunity to dissect the molecular pathways underlying normal alpha synuclein biology and the pathogenic consequences of its misfolding.

In sum, the invention described and claimed in the patent paves the way for the development of new drugs to help treat and prevent the development of Parkinson's disease; see, for example, Outeiro (**D19**), Willingham (**D20**) or Cooper (**D21**).

2.2 INVENTIVE STEP OF CLAIM 1 VIS-À-VIS WO 01/06989 (**D8**) AND OSTREROVA-GOLTS (**D9**)

2.2.1 THE TEACHING OF THE ALLEGED CLOSEST PRIOR ART DOCUMENT **D8**

Contrary to O's misreading and misinterpretation of **D8**, thereby neglecting the integral teaching of the document, **D8** discloses screening assays for identifying modulators which bind to a target protein that is capable of aggregation, such as alpha synuclein, and that alter the target protein's ability to interact with an intrabody (page 4, lines 16-25; page 26, line 2).

Generally, **D8** concerns methods for inhibiting polypeptide accumulation associated with neurological disorders. Accordingly, **D8** concerns a cell-based assay aimed at identifying a compound which **alters** the polypeptide/intrabody interaction.

Specifically, **D8** discloses on page 25, lines 36-38 a method for screening of compounds that **alter** the undesired accumulation, complexing, or aggregation of a selected polypeptide such as alpha synuclein by applying an intrabody.

However, the purpose of the screening assays is completely different from that referred to in claim 1, *i.e.*, for a compound that **decreases** alpha synuclein-associated toxicity.

As explained in section D.2.2, above it is an established principle in the EPO's jurisprudence that the purpose of a claimed method is a functional feature meaning that the method is suited for that very purpose which thus defines one of the method steps; see T 848/93.

On page 26, lines 11-15 of **D8** "a change in levels of cell death" is disclosed as read-out for an alteration in the intrabody/polypeptide interaction. However, claim 1 recites, in relevant part, that **viability** of yeast cells indicates whether the candidate compound decreases alpha synuclein-associated toxicity.

Accordingly, **D8**'s disclosure on page 26, lines 11-15 does not equate "evaluating the yeast cell for viability, wherein an increase in viability of the yeast cell as compared to viability of the yeast cell in the absence of the candidate compound indicates that the candidate compound decreases alpha synuclein associated toxicity".

In fact, this feature again distinguishes the claimed method from **D8** in that it provides a technical contribution, since the present inventors found that yeast cells expressing alpha synuclein (alone or in combination with a toxicity-inducing agent) can exhibit reduced viability. Accordingly, the viability of a yeast cell can be used to screen for a compound that decreases alpha synuclein-associated toxicity.

2.2.2 THE TEACHING OF THE PATENT

As already discussed above, the invention described in the patent is based, at least in part, on the inventors' discovery that yeast cells expressing alpha synuclein (alone or in combination with a toxicity-inducing agent) can exhibit reduced viability. This reduction in viability can be exploited to screen for compounds that alleviate toxicity resulting from alpha synuclein expression in yeast cells.

Accordingly, an understanding of the mechanism by which alpha synuclein contributes to a disease such as Parkinson's disease is neither critical nor required to put the claimed screening methods into practice. Rather, it is a distinct advantage of the claimed screening methods that a complete understanding of the mechanism of action of alpha synuclein is not required to identify useful compounds.

In sum, the invention is the finding that a yeast based screening model can be used to screen for compounds that are candidate therapeutics to help treat or prevent Parkinson's disease, whereby an understanding of the physiology and/or cell biology of the misfolded alpha synuclein disease protein or of the etiology of the misfolded protein disease is not necessary to identify these candidate therapeutics.

2.2.3 THE TECHNICAL PROBLEM TO BE SOLVED AND ITS SOLUTION

The technical problem underlying the claimed invention was not – as alleged by O – the provision of a "screening method wherein toxicity of the expressed alpha synuclein is ensured, which is of interest in the identification of compounds inhibiting alpha synuclein-mediated toxicity". Rather, the objective technical problem could be seen in the provision of a screening system suitable for the identification of candidate compounds to help treat or prevent alpha synuclein-associated protein misfolding diseases (such as Parkinson's disease), wherein the physiology and/or cell biology of the misfolded protein does not have to be known.

The solution is to use a polypeptide encoding human alpha synuclein protein in a yeast expression system for screening of candidate compounds to help treat or prevent alpha synuclein-associated protein misfolding diseases through the evaluation of the yeast cells' viability.

2.2.4 THE SKILLED PERSON

Applying the current standards of the EPO to the present case, the person skilled in the art can be defined as a cautious bench molecular biologist or a team of such persons being

familiar with the principles of recombinant DNA technology and expression of foreign proteins in cultured cells; see also decision T 455/91.

In view of O's hindsight interpretation of the prior art (which is not admissible as pointed out by the Board in T 455/91), it seems necessary to also point out that it is inappropriate to attribute the knowledge provided by the contested patent to the person skilled in the art in the analysis of inventive step.

2.2.5 THE CLAIMED METHOD IS INVENTIVE OVER **D8**

As pointed out in item 2.2.1, above, **D8** is irrelevant prior art with respect to the claimed method. In particular, **D8** does not teach a yeast based screening system, wherein an understanding of the physiology and/or cell biology of the misfolded protein does not have to be known. Furthermore, in striking contrast to the claimed invention, **D8**'s screening assays are directed at identifying compounds that alter the interaction of an intracellular antibody (intrabody) with a target polypeptide.

The investigation described in **D8** concerns a test to use intrabodies as a means of blocking the pathogenesis of Huntington's disease (HD) (e.g., Abstract; page 3, lines 11-16; and page 4, lines 16-25). HD is characterized by abnormally elongated polyglutamine near the N terminus of the huntingtin protein, which induces pathological protein-protein interactions and aggregate formation by huntingtin.

Specifically, selection from a human phage display library yielded a single-chain Fv (sFv) antibody specific for the 17 N-terminal residues of huntingtin, adjacent to the polyglutamine in HD exon 1. This anti-huntingtin sFv intrabody was tested in a cellular model of the disease in which huntingtin exon 1 had been fused to green fluorescent protein (GFP). Expression of expanded repeat HD-polyQ-GFP in transfected mammalian cells shows perinuclear aggregation similar to human HD pathology, which worsens with increasing polyglutamine length; the number of aggregates in these transfected cells provided a quantifiable model of HD for this study. Coexpression of anti-huntingtin sFv intrabodies with the abnormal huntingtin-GFP fusion protein dramatically reduced the number of aggregates, compared with controls lacking the intrabody. Anti-huntingtin sFv fused with a nuclear localization signal retargeted huntingtin analogues to cell nuclei, providing further evidence of the anti-huntingtin sFv specificity and of its capacity to redirect the subcellular localization of exon 1. This study suggests that intrabody-mediated modulation of abnormal neuronal proteins may contribute to the treatment of neurodegenerative diseases.

D8 uses as a test system COS-7 cells, *i.e.*, **mammalian** cells (see Example 1) in order to determine the effects of intracellular polypeptide aggregation in cells expressing a polypeptide from a Huntington's disease patient.

Moreover, **D8** employs **brain slices** for assaying polypeptide aggregation and effects exerted by the intrabodies generated in this patent application (see, e.g., page 26, line 30 to page 27, line 7; and Example 5).

Also, **D8** employs **animal models** for testing effects of the intrabodies (see Example 7).

It is obvious that **D8** uses mammalian cells, brain slices and animal models for screening purposes since these "systems", particularly brain slices and animal models closely resemble the naturally occurring situation as regards Huntington's disease. Indeed, the disease takes place in mammals and occurs in the brain.

Assuming *arguendo* that the skilled person would have taken into consideration some of **D8**'s suggestions, for example, to express alpha synuclein and screen for agents that alter undesired accumulation, complexing, or aggregation of a selected polypeptide such as alpha synuclein, s/he would not have applied non-mammalian systems such as yeast cells.

Alpha synuclein protein does not natively exist in yeast and it could therefore not have been expected that, as successfully shown in the instant patent, that alpha synuclein is adequately expressed in yeast.

Moreover, due to the complexity of neurological disorders caused by misfolded proteins, the skilled person would have assumed that an understanding of the mechanism by which alpha synuclein contributes to a disease such as Parkinson's disease is essential and would have required using a system that is as close as possible to the naturally occurring situation.

Furthermore, the skilled person knowing that alpha synuclein is toxic to neuronal cells when it aggregates would have expected alpha synuclein to exert this "behaviour" only in its natural environment, *i.e.*, in mammalian neuronal cells which contain all elements required for alpha synuclein aggregation. Hence, the skilled person would not have believed that alpha synuclein could exert cytotoxicity in yeast, since it (i) does not have an orthologue, let alone a homologue of alpha synuclein and (ii) most probably lacks cellular elements/structures which are present in mammalian neuronal cells.

Finally, until completion of the present inventors' work, the "misbehaviour" of alpha synuclein in a non-neuronal cell was unknown. Specifically, the reason as to why neuronal cells decline was unknown, since neither the molecular nor cellular or biological role of alpha synuclein was

known. Indeed, subsequent work continued on the basis of the present inventors' work elucidated a role of alpha synuclein. Specifically, the yeast expression system established by the present inventors facilitated the discovery that alpha synuclein overexpression in the yeast expression model inhibits phospholipase D, causes the production of reactive oxygen species, and problems in vesicle trafficking. The earliest defect following alpha synuclein induction in yeast was a block in vesicle trafficking from the endoplasmic reticulum (ER) to the Golgi. In a genetic screen to identify relevant biochemical pathways and targets the Rab GTPase Ypt1p was found. This finding was confirmed in an animal Parkinson's disease model in that elevated expression of Rab1, the mammalian YPT1 homolog, protects against alpha synuclein-induced dopaminergic neuron loss, and in cultures of rat midbrain. These results have demonstrated the relevance of results obtained in yeast to mammalian neurons. see Cooper (**D21**).

Of course, without the yeast expression system established by the present inventors, it would not have been possible to elucidate alpha synuclein's molecular, cellular and biological function.

Thus, without knowing the etiology of a misfolded protein disease, the skilled person would have refrained from using a system that is, at best, very distantly related to mammalian neuronal cells, *i.e.* yeast. In fact, yeast cells do not have a nervous system and thus lack neuronal cells.

Accordingly, the skilled person would not have thought that s/he can use yeast as a screening system in the absence of an understanding of the mechanism of action for discovering compounds that decrease alpha synuclein-associated toxicity. Thus, it would appear to be unexpected and surprising to observe that it is a distinct advantage of the claimed screening methods that a complete understanding of the mechanism of action of alpha synuclein is not required to identify useful compounds.

Even assuming *arguendo* that one of ordinary skill would have used yeast for some sort of experimentation, there would be no reason that the artisan would have considered contacting the yeast cell with a toxicity inducing agent as claimed by the patentee because the entire discussion in **D8** of testing for sensitivity to compounds such as excitotoxins is in the context of experimental animals or organotypic slice cultures derived from such animals (see, page 26, line 30 to page 27, line 7). There is simply no suggestion of using such assays in yeast cells.

Needless to say, in view of the deficient teaching of **D8**, **D9** adds nothing. All that **D9** reports is that iron increases aggregation of a known alpha synuclein variant (A53T). However, this teaching is utterly irrelevant since **D9** is concerned with the etiology of Parkinson's disease,

whereas the patent teaches that expression of alpha synuclein in yeast is toxic and that an understanding of the etiology of the disease is not required to screen for potential therapeutic compounds in yeast.

D9 attests to the fact that until the present inventors' work, the molecular, cellular and biological role of alpha synuclein was unknown (see the abstract of **D9**):

> "The mechanisms underlying PD are unknown, but the discoveries that mutations in synuclein can cause familial PD and that synuclein accumulates in Lewy bodies suggest that synuclein participates in the pathophysiology of PD".

In essence, **D9** demonstrates the present inventors' leap of faith to enter unpredictable areas when establishing yeast as screening system for compounds that may help treat or prevent protein misfolding diseases since, more or less, nothing was known about the molecular, cellular and biological role of alpha synuclein, let alone the etiology of protein misfolding diseases caused by alpha synuclein.

In view of the foregoing arguments, it is submitted that claim 1 is inventive over **D8** alone and the combined teaching of **D8** and **D9**.

2.3 INVENTIVE STEP OF CLAIM 9 VIS-À-VIS WO 99/29891 (D1) COMBINED WITH ENGELENDER (D10) OR OSTREROVA (D11)

2.3.1 THE TEACHING OF THE ALLEGED CLOSEST PRIOR ART DOCUMENT D1

D1 discloses a yeast system used in methods of identifying a candidate substance that inhibits the aggregation of an aggregate-prone amyloid protein (APAP), namely the PrP (the mammalian prion protein) and the beta-amyloid peptide 1-42 (the Alzheimer's disease protein).

Such methods comprise contacting a cell expressing APAP with a substance under conditions effective to allow aggregated amyloid formation, and determining the ability of the candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein (cf. page 3, line 18 to page 4, line 6). The aggregation of the APAP may be detected by the ability of the aggregated protein to bind to Congo Red or by increased protease resistance of the aggregated protein (see e.g., page 5, lines 13-15).

Regarding the teaching of the patent, the level of skill in the art and the objective technical problem and its solution, we refer to 2.2.2-2.2.4 above.

2.3.5 THE CLAIMED METHOD IS INVENTIVE OVER THE COMBINED TEACHING OF **D1** AND **D10** OR **D11**

In essence, **D1** reports that when purified Sup35 and Hsp104 are mixed, the circular dichroism (CD) spectrum differs from that predicted by the addition of the proteins' individual spectra, and the ATPase activity of Hsp104 is inhibited. Similar results are obtained with two other amyloidogenic substrates, mammalian PrP and β-amyloid 1-42 peptide, but not with several control proteins. With a group of peptides that span the PrP protein sequence, those that produced the largest changes in CD spectra also caused the strongest inhibition of ATPase activity in Hsp104. From these observations, the inventor of **D1** suggests that (i) previously described genetic interactions between Hsp104 and [*PSI+*] are caused by direct interaction between Hsp104 and Sup35; (ii) Sup35 and PrP, the determinants of the yeast and mammalian prions, respectively, share structural features that lead to a specific interaction with Hsp104; and (iii) these interactions couple a change in structure to the ATPase activity of Hsp104 (see page 3, lines 18-30 of **D1**).

Thus, the inventor of **D1** seems to suggest that protein chaperones provide common mechanisms for controlling certain types of conformational switches and, thus, might provide potential avenues for therapeutic intervention. It is in this context that the disclosure with respect to yeast cells in **D1** should be considered.

Specifically, the inventor of D1 suggests that "yeast cells provide an excellent system for testing and manipulating the folding state of amyloid proteins, which is useful in identifying therapeutic agents" (see page 31, lines 12-15, emphasis added). With respect to the invention therein, **D1** states that it "demonstrates that yeast cells provide a system in which the folding of amyloidogenic proteins from diverse organisms is subject to manipulation" and that "the inventor contemplates that the formation of amyloid fibers may be detected by a number of mechanisms" (see page 9, lines 26-27 and page 10, lines 25-26).

Yet, the present inventors teach that expression of alpha synuclein in yeast is toxic and hence viability screens may be performed in yeast (to identify potential therapeutics for alpha synuclein-associated diseases) that require no understanding of the mechanism of action of alpha synuclein.

D1 does not suggest that a screening system based on alpha synuclein may be performed that does not necessitate an understanding of the physiological and/or cell biology of the protein misfolding disease.

Furthermore, neither the endogenous yeast prion protein Sup35 nor the β-amyloid 1-42 peptide is shown by **D1** to be toxic to yeast cells. Thus, the skilled person would not have thought that alpha synuclein could cause toxicity in yeast cells, let alone that viability of yeast

cells could be used as read-out in screening for compounds that decrease alpha synuclein-associated toxicity.

More specifically, **D1** discusses at page 11, lines 12-18 that a chimeric protein that comprises a Sup35 C-terminal domain in combination with an amyloidogenic protein, *i.e.*, a fusion protein could be used for screening candidate compounds for their ability to inhibit β-amyloid aggregation in a yeast having a [PSI+] genetic background, *i.e.*, a [PSI +] phenotype.

This is so, because a yeast cell expressing this chimeric fusion protein has a [PSI+] phenotype, if the fusion protein aggregates, that leads to cell death. Accordingly, a compound that inhibits β-amyloid aggregation could reverse β-amyloid aggregation and, thus, prevent yeast cells from cell death.

However, the principle of the screening assay suggested in **D1** is fundamentally different from that embodied by claim 9.

Indeed, claim 9 assesses "alpha synuclein-associated toxicity" and does not require chimeras with Sup35 in order to effect cell death in yeast cells. While O quotes from page 11, lines 12-18 of **D1** on page 9 of the brief, this passage relates to chimeric proteins that comprise Sup35 in combination with an amyloidogenic protein, but claim 9 does not require such a fusion. In the absence of such a fusion, the viability assay described in **D1** would not work because it is the sequestration of the C-terminal region of Sup35 that causes the [PSI+] phenotype. Furthermore the mere fact that the β-amyloid (1-42) + Sup35 C-terminus has a [PSI+] phenotype that leads to cell death does not indicate that alpha synuclein in such a chimera would cause cell death.

In contrast, in the method of claim 9, alpha synuclein alone is sufficient to cause cell death which, in view of **D1**, could not have been expected. In fact, it is known and taught in **D1** that an amyloidogenic protein (*i.e.*, a protein involved in a protein misfolding disorder) alone is not toxic to yeast cells. Thus, a skilled person would not have had a reasonable expectation of success in expressing alpha synuclein alone in a yeast cell with the aim of establishing a screening system for compounds that decrease alpha synuclein-associated toxicity.

Neither **D10** nor **D11** remedy the deficiencies of D1, because neither of these references point to the solution of the viability-based assay system of the claimed invention.

D10 cannot supplement the teaching of **D1** so as to arrive at the claimed method. In fact, **D10** is totally irrelevant for assessing inventive step and, therefore, the skilled person would not combine **D1** and **D10** and use the yeast system described in **D1** to screen for agents useful, for example, in treating alpha synuclein associated diseases such as Parkinson's disease.

Indeed, all that **D10** contributes to the art is the identification of a protein (synphilin-1) which associates with alpha synuclein. Synphilin-1 was found in a yeast two hybrid screen. However, **D10** is totally silent about the fact that expression of alpha synuclein in yeast is toxic or that a yeast cell expressing alpha synuclein can be used in a viability assay to screen for potential therapeutic compounds. There is no indication in **D10** that a screening method based on alpha synuclein would not necessitate knowledge of the physiology and/or cell biology of the protein misfolding disease.

On the contrary, **D10** attests to what has been explained before: the molecular, cellular and biological role of alpha synuclein was unknown prior to the present inventors' work; see the abstract of **D10**:

> "It is unknown how synuclein contributes to the cellular and biochemical mechanisms of PD, and its normal functions and biochemical properties are poorly understood."

Hence, the skilled person would not consider **D10** as promising when s/he would have been curious to identify compounds that help treat or prevent alpha synuclein associated diseases. In fact, the skilled person would first continue the work of **D10** in finding out normal functions of alpha synuclein and subsequently its pathophysiological role.

For the reasons given in item 2.2.5, above, the skilled person would not have used yeast as a model system for exploring alpha synuclein function, let alone as a tool for screening therapeutic agents.

Likewise, **D11** adds nothing. **D11** reports that alpha synuclein interacts with various proteins such as 14-3-3 proteins, protein kinase C (PKC), an extracellular regulated kinase (ERK) involved in the ERK MAP kinase pathway of mammalian cells including Raf protein and BAD (a Bcl-2 homologue) (see Abstract and page 5785).

Indeed, **D11** teaches away from the invention by directing the skilled person to refrain from separating alpha synuclein from its natural environment (mammalian neuronal cells) into a yeast, which does not have BAD. Moreover, although yeasts have ERKs, these ERKs are not involved in the same pathways in mammalian cells, *i.e.*, yeast does not have an ERK MAPK pathway involving ERK and Raf.

In essence, like **D9**, **D11** demonstrates the present inventors' leap of faith to enter unpredictable areas when establishing yeast as a screening system for compounds that may help treat or prevent protein misfolding diseases since, more or less, nothing was known

about the molecular, cellular and biological role of alpha synuclein, let alone the etiology of protein misfolding diseases caused by alpha synuclein.

In view of the above, claim 9 is inventive over the combined teaching of **D1** and **D10 or D11**.

2.4 INVENTIVE STEP OF CLAIM 9 VIS-À-VIS WO 99/06545 (**D12**) AND WO 01/06989 (**D8**)

2.4.1 THE TEACHING OF THE ALLEGED CLOSEST PRIOR ART DOCUMENT **D12**

O alleges that **D12**, in essence, provides a "method of screening for an inhibitor of aggregate formation comprising the steps of

- providing a yeast cell engineered to express a polypeptide comprising alpha synuclein, and
- contacting the yeast cell with a candidate compound".

However, when analyzing the passages from which O quotes in detail, it is apparent that O misinterprets and misunderstands **D12**.

Page 15, lines 20-28

> Further, the present invention relates to a method of testing a prospective inhibitor of aggregate formation of a fusion protein as defined in the composition of the invention when enzymatically or chemically cleaved or a non-cleaved fusion amyloidogenic (poly)peptide as defined hereinbefore or an amyloidogenic non-fusion (poly)peptide comprising
> (a) incubating in the presence of a prospective inhibitor
> (aa) said fusion protein in the presence or absence of a cleaving agent; or
> (ab) said non-fusion poly(peptide); and
> (b) assessing the formation of amyloid-like fibrils or protein aggregates.

Reading the remainder of the above quoted passage reveals the "true" disclosure of **D12** (see page 15, lines 30-33)

> This method of the present invention provides a particularly strong impact on the pharmaceutical research related to amyloid-associated diseases. For the first time, an inhibitor of fibril or aggregate formation can conveniently, directly, easily and within a short time be tested *in vitro*. As has been detailed herein above, aggregate formation may be tested on cleavage products, on non-cleaved fusion proteins or on the above recited non-fusion proteins which have the capacity to aggregate when the temperature is raised, the pH is lowered or the protein is dissolved in urea and the urea is slowly diluted out with a solvent. Additionally, the present invention does not exclude self-assembly under different conditions.

Thus, **D12** relates to an *in vitro* method.

Consequently, O's quotes to claim 1 (composition comprising a host expressing the fusion protein), claim 7 (alpha synuclein) and claim 11 (yeast as a host cell) are taken out of context. Indeed, **D12** never envisages an *in vivo* screen.

O also quotes:
Page 3, 1st paragraph, last sentence

> Thus, the mechanism underlying HD would be similar to scrapie, Creutzfeldt-Jakob or Alzheimer's disease, in which β-sheet secondary structures lead to the formation of toxic protein aggregates in selective neurons (Caughey and Chesebro, 1997).

O's reference to this passage is not very helpful. The patent does not teach that alpha synuclein is related to Alzheimer's disease.

The above being said, the "true" teaching of **D12** is a test protein for elucidating amyloid-like fibril or protein aggregate formation. This is immediately apparent from page 5, lines 13-20.

> In accordance with the present invention, it could surprisingly be shown that the composition comprising the above recited components can be used for the elucidation of amyloid-like fibril or protein aggregate formation. The components of the composition can be used in varying combinations to test, for example, for specific conditions under which amyloids are formed *in vitro*. The *in vitro* data obtained with the composition of the invention may then be compared to or brought into relation with the *in vivo* situation and appropriate conclusions may be drawn therefrom.

Regarding the teaching of the patent, the level of skill in the art and the objective technical problem and its solution, we refer to 2.2.2-2.2.4 above.

2.4.5 THE CLAIMED METHOD IS INVENTIVE OVER THE COMBINED TEACHING OF **D12** AND **D8**

For the reasons given in item 2.4.1, above, **D12** does not qualify as the closest prior art document.

However, even if *in arguendo* we assume that **D12** is the closest prior art document, it cannot render obvious the method of claim 9. In fact, **D12** teaches *in vitro* methods, while claim 9 is an *in vivo* method (cf. host cell expressing alpha synuclein). For this reason alone, **D12** teaches away from the claimed method.

D8 does not remedy the deficiencies of **D12** for the reasons given in item 2.2.5, above.

In this regard, we point out that the only quote to which O refers in the context of its allegation from "**D8**", *i.e.*, page 21, lines 30-33 reads:

> Accordingly, such an intrabody could inhibit the accumulation, formation of aggregates, or retarget the cellular localization, of several forms of an altered polypeptide if each form had a minimal polyglutamine rich region. However, specificity for the unique class of polypeptides of interest, *e.g.* huntingtin, preferably requires a bispecific or multi-specific sFv antibody or diabody or related forms of the Fv, wherein additional specificity is conferred for non-polyglutamine, polypeptide-specific epitopes The diabody is a bivalent or bispecific, or

This quote does not reflect what Opponent alleges, namely:

> This problem is solved in D8. Indeed, as indicated above, D8 in fact generally discloses screening methods encompassed by claim 9. Moreover however, D8 particularly specifies that "the ability of the polypeptides to aggregate in the presence of the compound is determined by measuring viability in the presence of a selection agent" (page 21, lines 30-33). It is further specified in this context that "an increase in cell viability in the presence of a test compound plus selection agent, compared to the selection agent alone, is an indication that the test compound is an aggregation disrupting polypeptide".

Yet, O's quote is apparently taken from **D7** (see page 20, line 29, to page 21, line 6):

> that cell during selection. Thus, where a selectable marker is used, the ability of the polypeptides to aggregate in the presence of a compound is determined by measuring cell viability in the presence of a selection agent, e.g., an antibiotic. For example, where the selection marker is *neo*, the selection agent aminoglycoside G-418 can be used, or where the selectable marker is hygro, the selection agent is typically hygromycin. An increase in cell viability in the presence of a test compound plus selection agent, compared to the selection agent alone, is an indication that the test compound is an aggregation disrupting polypeptide.

However, **D7** is totally irrelevant, since it was published later than the filing date of the patent (and is not even prior art under Article 54(3) EPC, as already discussed above). In any case, the passage from which O has cited is again taken out of context. Specifically, O alleges that "an increase in cell viability in the presence of a test compound plus selection agent, compared to the selection agent alone, is an indication that the test compound is an aggregation disrupting polypeptide" would be relevant with regard to the functional feature given in the "wherein clause" of claim 9.

Yet, the quote referred to by O concerns the use of a label in a screening system. In detail, aggregation of a polypeptide fused to a selectable marker in a cell can inhibit the ability of the selectable marker to confer antibiotic resistance on the cell during selection; see page 20, lines 26-29 of **D7**:

> The aggregation of polypeptides fused to selectable markers in a cell inhibits the ability of the selectable marker to confer antibiotic resistance on that cell during selection.

Needless to say that this has nothing to do with the functional feature given in claim 9.

In sum, O's attempt to challenge inventive step of claim 9 or the basis of the combined teaching of **D12** and **D8** (or **D7**, which in any case cannot be combined as prior art) is totally flawed, both from a legal point of view with respect to substantive patent law and from a scientific point of view.

2.5 INVENTIVE STEP OF ALL CLAIMS VIS-À-VIS WO 99/29891 (**D1**), WO 01/06989 (**D8**), OSTREROVA (**D11**), WO 99/06545 (**D12**), KROBITSCH (**D13**) OR LIU (**D14**)

2.5.1 THE TEACHING OF **D1, D8, D11, D12, D13** AND **D14**

In a final attempt, O wishes to use almost each and every document on file, most of which have been used in preceding attempts to challenge inventive step, to attack inventive step.

This final attempt, however, has nothing to do with the established problem-solution approach of the EPO. In any case, the arguments have no merit.

The insignificance of **D1**, **D8**, **D11** and **D12** for assessing inventive step has been demonstrated in items 2.2-2.4, above.

Regarding **D13** and **D14**, we note that neither of these documents, individually or taken together, conceives, develops or reduces to practice a yeast cell based assay system, whereby an understanding of the physiology and/or cell biology of the misfolded disease protein or of the etiology of a protein misfolding disease is not necessary to identify candidate therapeutic compounds for treating or preventing, for example, Parkinson's disease.

2.6 THE TECHNICAL PROBLEM IS SOLVED OVER THE WHOLE BREADTH OF CLAIM 9

2.6.1 In item 3.4.2 of its brief, O contends that claim 9 would not solve the technical problem over the whole breadth of the claim, since no toxicity-inducing agents or conditions are specified and, thus, yeast cells would not undergo cell death induced by alpha synuclein toxicity and, thus, a screening for useful agents would be impossible.

O further alleges that thus claim 9 encompasses "methods whereby other types of toxic agents are added to the cells". Consequently, the effect of such an agent could not be linked to a decrease of alpha synuclein-induced toxicity.

2.6.2 Once more, O's contention must fail.

As explained in section G.2, below, the data contained in the present patent clearly demonstrates that expression of alpha synuclein alone is toxic in yeast cells. Thus, no additional toxicity inducing compounds are required (see, e.g., Figure 3, Example 11, and page 10, lines 30-33 of the patent). Accordingly, compounds which "reverse" (fully or partially), i.e., decrease, alpha synuclein-induced toxicity in a yeast cell are *per se* candidate compounds.

Consequently, claim 9 contains all elements required to perform the claimed method and, thus, it solves the technical problem underlying the invention.

F. THE GRANTED CLAIMS ARE SUSCEPTIBLE OF INDUSTRIAL APPLICATION (ARTICLE 57 EPC)

1. In item 3.5 of its brief, O alleges that claims 1 and 9 could not be considered susceptible of industrial application. With respect to claim 1, O alleges that it claims a result to be achieved. Regarding claim 9, O alleges that "the characterizing features of the method itself are not disclosed and the result is merely defined by the object of the process" so that claim 9 is "an example of circular reasoning".

2. O's allegations are flawed and completely miss the point.

The law, *i.e.*, Article 57 EPC requires that

> *"An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture."*

Rule 42(1)(f) EPC requires that the description shall

> *"indicate explicitly, when it is not obvious from the description or nature of the invention, the way in which the invention is industrially applicable."*

The case law requires that the key question for the assessment of compliance with the requirements of Article 57 EPC is whether the invention as disclosed in the application was "susceptible of industrial application".

The case law indicates that the notion of "industry" had to be interpreted broadly to include all manufacturing, extracting and processing activities of enterprises that were carried out continuously, independently and for financial (commercial) gain (see, e.g. T 144/83). The requirement of Article 57 EPC that the invention "can be made or used" in at least one field of industrial activity emphasized that a "practical" application of the invention has to be disclosed.

The patent and, particularly, the claimed methods comply with the requirements of the law and are in line with case law on industrial application.

Specifically, both claim 1 and claim 9 relate to a method for screening for a compound that decreases alpha synuclein-associated toxicity.

It was known before the earliest filing date of the patent that alpha synuclein is abundant and broadly expressed in the brain. Alpha synuclein is implicated in several neurodegenerative disorders such as Parkinson's disease (PD) and multiple system atrophy. Alpha synuclein over-expression is thought to contribute to the decay of nerve cells. Two point mutations of alpha synuclein (A53T and A30P) are known to be associated with rare forms of early-onset familial PD (see patent on page 3, [0005]).

Hence, finding compounds which could modulate, *e.g.*, interfere with alpha synuclein toxicity, is highly desirable, since such compounds could be potential candidates for developing medicaments against diseases caused by alpha synuclein.

Indeed, there is strong evidence that links the misfolding of alpha synuclein to Parkinson's disease.

Therefore, the claimed methods of claim 1 or 9 can be made and used in pharmaceutical industry for identifying potential candidate compounds useful for treating or preventing diseases caused by alpha synuclein induced toxicity. This is all that the law and the EPO's jurisprudence requires.

The above being so, we note that – contrary to O's flawed allegations - neither the law nor the case law in the context of industrial application says anything about "a result to be achieved" or "circular reasoning" as O did when alleging that claims 1 and 9 would not be susceptible to industrial application.

Hence, for this reason alone, O's allegations must fail. Even more, O has not provided any evidence that the methods of claim 1 or 9 would not be susceptible of industrial application.

On the contrary, as explained above, the claimed methods are susceptible of industrial application, since they can be made and used in any kind of industry, particularly in pharmaceutical industry, as is required by the law.

Consequently, O's allegations are without merit.

As an aside, O's allegations appear to be made in view of Article 84 EPC, since O uses typical wording for making objections under Article 84 EPC, *i.e.*, "result to be achieved" and "circular reasoning". However, Article 84 EPC is not available as a ground for opposition.

That being so, for the sake of completeness, we submit that neither is claim 1 a "result to be achieved" nor is claim 9 a "circular reasoning."

In fact, claim 1 contains all elements required to achieve the goal (*i.e.*, the purpose) of the claimed method.

A yeast cell expressing alpha synuclein is contacted with a candidate compound and with a toxicity-inducing agent and is evaluated for viability. An increase in viability indicates that the candidate compound decreases alpha synuclein-associated toxicity.

Likewise, claim 9 is not a "circular reasoning". For the same reasons, *mutatis mutandis*, as to why claim 1 is not a "result to be achieved", claim 9 is not a "circular reasoning", since it contains all elements required to solve the "purpose" of the claimed method.

G. THE GRANTED CLAIMS ARE SUFFICIENTLY DISCLOSED (ARTICLE 83 EPC)

1. In item 3.6 of its brief, O contends that claim 9 would be insufficiently disclosed, since the claimed method cannot be carried out over the whole range claimed. Specifically, O contends that the level of expression of alpha synuclein is important insofar as low level expression would not result in aggregate formation, while expression at a level resulting in aggregate formation is toxic for a cell. Accordingly, O contends that the claim is missing an additional feature such as control of alpha synuclein expression by an inducible promoter, presence of a toxicity inducing agent or co-expression of a heat shock protein.

2. Again, we disagree.

The application underlying the patent teaches that

> The present invention is based on the observation that proteins that misfold and are associated with a disease ("misfolded disease protein") can be expressed in yeast as the basis for screening for therapeutic agents for the treatment of such a disease. Conditions and/or agents have been identified that induce toxicity ("toxicity inducing agent") in a yeast cell expressing a misfolded disease protein, such as huntingtin or alpha synuclein, which are associated with Huntington's disease and Parkinson's disease, respectively.
> [page 3, lines 17-22].

Furthermore, the application teaches

> associated with the misfolded disease protein. The screen uses viability of the yeast, which express a misfolded disease protein and in which toxicity is induced, to identify compounds that have therapeutic potential in the treatment of the disease associated with the misfolded disease protein. An advantage of the screening methods is that an understanding of the physiology and/or cell biology of the misfolded disease protein or of the etiology of a misfolded protein disease is not necessary to identify candidate therapeutic compounds.
> [page 3, lines 27-32].

In sum, the application teaches that an understanding of the physiology and/or cell biology of the misfolded disease protein (alpha synuclein) or of the etiology of a misfolded protein disease is not necessary to identify candidate therapeutic compounds.

Rather, the application teaches that viability of yeast cells can be used as a read-out in screening for candidate compounds which may be used for treating or preventing Parkinson's disease.

Indeed, on page 11, lines 15-22, the application discloses

> The present inventors have developed a system which allows the rapid identification of candidate therapeutic agents that prevent and/or inhibit the process of protein aggregation leading to fibrillogenesis and protein deposition. The system is a yeast-based system, wherein a yeast cell is engineered to expresses a protein or polypeptide that is involved in fibril formation, for example, the yeast cell can express a huntingtin polypeptide in the case of Huntington's disorder, or expresses an alpha synuclein polypeptide in the case of Parkinson's disease, or express an amyloid protein in the case of a disease involving amyloidoses (also see Table 1 for a list of proteins that are associated with fibril formation).

and that

> A decrease or inhibition of growth indicates toxicity of the recombinant fibril forming polypeptide in the yeast cell as a result of some change in expression or activity of other proteins or cellular factors that interact with the recombinant fibril polypeptide due to the change in genetic background. This cytotoxic profile is correlated to human and/or other mammalian neurodegenerative state. Thus, if such a yeast cell is exposed to a candidate substance, one can screen for the potential of the agent to reverse cytotoxicity, which correlates to the ability of the agent to prevent cytotoxic and/or neurotoxic protein aggregation and fibril formation.
> [page 11, lines 26-33].

More specifically, in Figure 3 it is shown that alpha synuclein fused to GFP under the control of the GAL1-10 promoter is toxic to yeast cells. Similar results were also observed with alpha synuclein alone (page 10, lines 30-32).

Accordingly, as is stated on page 10, lines 32-33 of the application:

> These assays have been used in the screening methods to identify agents that can alleviate the observed toxicity.

Hence, the skilled person knows that alpha synuclein can be toxic to yeast cells and would therefore know that an appropriate promoter has to be chosen in order to make use of the inventors' finding that viability is the read-out for identifying a compound that decreases alpha synuclein-associated toxicity.

Indeed, knowing from the application that expression of alpha synuclein in yeast cells is toxic, the skilled person would rule out using conditions which would not allow performing the claimed method. Putting it differently, the skilled person would rule out illogical embodiments; see the catchwords of T 190/99, *i.e.*, "the skilled person when considering a claim should rule out interpretations which are illogical or which do not make technical sense."

Figure 3 of the patent shows that a marked growth inhibition was observed in yeast cells expressing wild-type alpha synuclein or a mutant alpha synuclein. In the experiments depicted in Figure 3, the yeast cells contained a vector with either wild-type or a mutant alpha synuclein placed under the control of a galactose-inducible promoter. As a result, alpha synuclein expression was induced (which expression was toxic to the yeast) only when the yeast was cultured in galactose-containing medium. The patent notes (at page 28, lines 10-13) that yeast growth assays such as those depicted in Figure 3 may be used in screening methods to identify agents that can alleviate the toxicity observed in yeast expressing alpha synuclein.

Claim 9 is directed to a method of screening for a compound that decreases alpha synuclein-associated toxicity. The claimed method identifies such a compound by selecting a compound that results in an increased viability of a yeast cell expressing alpha synuclein.

The results depicted in Figure 3 are a demonstration that alpha synuclein expression results in toxicity in yeast cells (the assays depicted in Figure 3 were carried out without the use of an accompanying "toxicity inducing agent"). As a result, it would have required no undue experimentation for a person of ordinary skill in the art to use yeast cells expressing alpha synuclein (e.g., a yeast cell depicted in Figure 3) under the control of an appropriate promoter in the method of screening of claim 9.

An appropriate promoter is, for example, an inducible promoter which allows suppressing alpha synuclein expression so that yeast cells grow and also allows inducing alpha synuclein expression under inducing conditions.

Moreover, on pages 32-34 the application teaches promoters, such as inducible promoters.

The skilled person is therefore equipped with more than sufficient guidance regarding which promoter could be used in performing the claimed method so that yeast cells get sick from the expression of alpha synuclein. However, a candidate compound would reverse the cytotoxic effect of alpha synuclein which translates into an increase in the viability of yeast cells.

For the sake of completeness, we note that in accordance with the established jurisprudence of the EPO it is not necessary that a claim provides a detailed recipe about how a method has to be performed. Accordingly, we would like to refer to decision T 61/94, where the Board noted:

> "Article 84 when read in conjunction with Rules 29(1) and (3), has to be interpreted as meaning not only that an independent claim must be comprehensible from a technical point of view but also it must define clearly the object of the invention, that is to say indicate all the essential features thereof."

Indeed, T 61/94 makes it clear [as regards the presence of essential elements] that

> "this does not mean, however, that a claim must describe the invention in all its details".

It is self-explanatory that The Board's reasoning is also applicable in view of Article 83 EPC, since in the case discussed in T 61/94 the point for discussion under Article 84 EPC was support and the Guidelines for Examination rule in C-III, 6.4 that "although an objection of lack of support is an objection under Article 84 EPC, it can often [...] also be considered as an objection of insufficient disclosure of the invention under Article 83 EPC".

Another example that not all features of a method must be present in a claim is decision T 1055/92. The Board stated that the content of claims is governed by the requirements of Article 84 and Rule 29 EPC 1973. As to Article 84 and Rule 29 EPC 1973, the Board saw only two categories of "essential features"; those expressly stated in the description as being essential and those essential to distinguish the invention from the prior art. The Board made it clear that the latter set of essential elements may and usually will change during examination as prior art comes to light.

T 990/99, another decision discussing the presence or absence of essential features in a claim contains the helpful statement that

> "[t]he limiting features necessary to define the invention in the claims will always depend on the closest prior art. When there are not references or only weak ones cited in the case, it is obvious that an independent claim can be very generally formatted, i.e. the essential features can be stated in a generalized form".
> [Emphasis added]

The view of the Board of Appeal is applicable to the present case, where there is no such prior art document to which the claimed invention would have to be limited by introducing one more "essential" features. In fact, the prior art did neither disclose nor teach that yeast cells *per se* can be used in screening methods for compounds that decrease alpha synuclein-associated toxicity, whereby viability of yeast cells is used as read-out.

Consequently, there is – contrary to O's assertion – no need that claim 9 must require the yeast cells to (i) co-express hsp40, (ii) express a mutant form of alpha synuclein, or (iii) express alpha synuclein under the control of an inducible promoter.

Finally, Example 11 to which O refers and which allegedly demonstrates that either a toxicity inducing agent or an inducible promoter is a prerequisite for performing the claimed method do not at all attest to O's allegation. Rather, Example 11 reports about over-expression of alpha synuclein and that candidate compounds alleviated toxicity. This means that yeast cells which already over-express alpha synuclein are viable and may do even better after having been in contact with a candidate compound.

Hence, contrary to O's allegations, such yeast cells are viable for a time sufficient to permit screening for a compound which decreases alpha synuclein-associated toxicity.

Otherwise, a compound could not have alleviated alpha synuclein-associated toxicity.

In sum, O's assertions are flawed and, more importantly, O did not provide evidence that its assertions are substantiated. However, it is the standard for a party alleging lack of sufficiency of disclosure to present serious doubts that the claimed invention could not be reduced to practice without undue burden that are substantiated by verifiable facts (T 19/90).

Thus, O's assertions are without merit, and claim 9 complies with Article 83 EPC.

H. SUMMARY

- We have demonstrated that claims 1 and 9 find a basis in the application as filed, thereby complying with the requirements of Article 123(2) EPC (see section B).

- We have demonstrated that claim 9 is novel over the prior art documents cited by O (see section D).

- We have demonstrated that all claims are inventive over the prior documents cited by O (see section E).

- We have demonstrated that the claimed invention is susceptible to industrial application and is sufficiently disclosed (see sections F and G).

Accordingly, our request that the opposition is to be rejected and the patent be maintained as granted is fully justified.

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Enclosures
Annex A
Documents D15-D21

SP/GW/KH

Opposition against European patent EP 1 392 849 (Application No. 02 718 994.3) **ANNEX A**
Title: Yeast screens for agents affecting protein folding
Proprietor: University of Chicago
Opponent: reMynd N.V.
Our Ref.: UCH13189OP

Consolidated list of documents

Document	Title	Bibliography
D1	WO 99/29891	*Publication:* June 17, 1999
D2	US 5,547,841	*Publication:* August 20, 1996
D3	US 5,652,092	*Publication:* July 29, 1997
D4	WO 91/04339	*Publication:* April 4, 1991
D5[1]	Masison and Wickner, *TIGS*, **12**: 14	January 1996
D6	Tuite and Lindquist, *TIGS*, **12**:467-471	
D7	WO 01/23412	*Priority Date:* September 27, 1999 *Filing Date:* September 27, 2000 *Publication:* April 5, 2001
D8	WO 01/06989	*Publication:* February 1, 2001
D9	Ostrerova-Golts *et al.*, *J. Neuroscience*, **20** :6048-6054	August 2000
D10	Engelender *et al.*, *Nat. Genetics*, **22**:110-114	May 1999
D11	Ostrerova *et al.*, *J. Neuroscience*, **19**:5782-5791	July 1999
D12	WO 99/06545	*Publication:* February 11, 1999
D13	Krobitsch *et al.*, *Proc. Natl. Acad. Sci. USA*, **97**:1589-1599	February 2000
D14	Liu *et al.*, *Nature*, **400**:573-576	August 1999
D15	EPO form 1205A (01.02) pertaining to EP 00 977 270 (i.e., D7)	July 2002
D16	EPO Form 1303 (11.97)	October 2002
D17	Temussi *et al.*, *Embo J.*, **22**:355-361	January 2003
D18	Koo *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**:9989-9990	August 1999
D19	Outeiro and Lindquist, *Science*, **302**:1772-1775	December 2003
D20	Willingham *et al.*, *Science*, **302**:1769-1772	December 2003

[1] The Article in TIGS is merely a digest of the original Article published in *Science*, **270**:93-95

D21	Cooper *et al.*, *Science*, **313**:324-328	July 2006